UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,569	07/31/2006	Thomas Cappola	P-7627-US	6921

49443 7590 06/26/2009

Pearl Cohen Zedek Latzer, LLP
1500 Broadway
12th Floor
New York, NY 10036

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
06/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,569	CAPPOLA ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *16 and 19-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-30 are pending.
Claims 16, and 19-30 are withdrawn from examination as detailed below.
Claims 1-15, 17 and 18 are examined on the merits.

Please note that the Examiner handling this application has changed and is now Stephen Kapushoc in Art Unit 1634. Please address any future correspondence concerning this application to the above named Examiner.

Election/Restrictions

1. Applicant's election of the invention of Group 1 (claims drawn to method for predicting rejection) in the reply filed on 04/29/2009 is acknowledged. Applicants further elections are also acknowledged as follows: the particular combination of genes with increased expression of UQCRB, BTF3, ST13, and CUL4A; the particular gene with decreased expression of CFLAR; and the particular EST of SEQ ID NO: 12. It is noted that the Requirement for Restriction of 04/02/2009 required an election of either cardiac or allograft, where Applicants have elected cardiac; upon examination of the application this requirement is **WITHDRAWN** (withdrawal of this portion of the Requirement for Restriction does not effect any other Restriction Requirements as set forth in the requirement of 04/02/2009). Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 16 and 19-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (i.e.: claim 16 requires genes with increased expression other than the elected combination of UQCRB, BTF3, ST13, and CUL4A; claims 19-39 are drawn to non-elected products), there being no allowable

generic or linking claim. Election was made **without** traverse in the reply filed on 04/29/2009.

Claim Objections

3. Claims 2 and 4 objected to because of the following informalities:

Claims 2 and 4 are objected to over recitation of gene symbols without the full name of the gene, where in the first instance of a gene symbol in the claims the symbol should be accompanied by the full gene name, for example 'where said increased expression is measured for UQCRB (ubiquinol-cytochrome c reductase binding protein)'.

Claims 2, 4 and 9 are objected to over the recitation of non-elected subject matter in the alternative. Applicants have elected for the examination of methods as they require the particular combination of specific genes of UQCRB, BTF3, ST13, and CUL4A (increased expression), CFLAR (decreased expression), and SEQ ID NO: 12 (EST sequence). It is noted that claim is found allowed in this Office Action. Prior to the allowance of any claim, subject matter that has not been re-joined with the elected subject matter will be required to be removed from the claims.

Appropriate correction is required.

Objection to the Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example pages 27, 28, 29 and 35 of the specification. Applicants should thoroughly inspect the specification in its entirety to remove any other instances of hyperlinks. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

5. The disclosure is objected to because of the following informalities: The specification recites the phrase ' [Is this correct?] ' lines 17-18 of page 28, which appears to be a typographical error.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-15, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims are drawn to methods for predicting transplant rejection (independent claim 1) and methods for identifying a candidate (independent claim 16), but have only the single active process step of determining a gene expression profile, where simply determining a profile does not render a prediction of identify a candidate. The claims may be made more clear to

require steps of comparing a subject gene expression profile to a standard profile, and correlating some particular difference in gene expression with transplant rejection.

8. Claims 14, 15, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims depend from claim 15, where claim 15 recites 'the method of claim 15'. As such claim 15 is dependent upon itself and the metes and bounds of the claims, and thus the claims which depend from claim 15, are unclear. In the instant case, as the metes and bounds of the claims are entirely unclear no reasonable interpretation of the claims can be established, and as such the claims are not further rejected in this Office Action.

Claim Rejections - 35 USC § 112 1st ¶ - Enablement

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The claims are drawn to methods for detecting tissue rejection generically comprising the analysis of expression of at least four over expressed and at least one under expressed genes as compared to a standard.

The claims are drawn to methods particularly comprising (as consonant with the Election) analysis of expression of UQCRB, BTF3, ST13, CUL4A, CFLAR, and SEQ ID NO: 12.

The claims encompass the detection of any level of gene expression, and comparison to any profile used as a standard; for example expression that is increases as compared to any level.

The claims encompass the detection of rejection of any type of tissue in any subject organism.

The claims encompass the analysis of gene expression in any tissue, and the analysis of rejection of any tissue type.

The claims thus require knowledge of a correlation between any level of gene expression of any generic gene, in any tissue sample type, in any subject organism and the presence of tissue rejection of any tissue type.yup

Direction provided by the specification and working example

The instant specification provides an analysis of human gene expression peripheral blood samples (p.26-27) in three populations of cardiac transplant subjects: (1) non-rejecting transplants (control); (2) actively rejecting transplants (rejection); and (3) rejection subjects following immunosuppression treatment to alleviate rejection (post-rejection). The specification teaches that in an analysis of gene expression in 7

controls, 7 rejection, and 7 post-rejection subjects (p.27) using the Affymetrix HU133A array, 91 candidate genes demonstrating differential expression between rejecting and non-rejecting subjects were identified (p.28). The specification further teaches that 40 transcripts were selected for classification of samples using hierarchical clustering (p.32-33; Figure 3), and asserts that the 40 genes are disclosed in Table 2 of the specification.

Relevant to the breadth of the rejected claims, the specification does not teach an analyses of non-cardiac tissue rejection, gene expression in non-blood samples, analysis of non-human samples, or the reliability of classification methods using less than the complete set of genes analyzed for the cluster analysis.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the analysis of mRNA expressed in any sample is high, the unpredictability in associating any gene expression level with a phenotype such as tissue rejection as encompassed by the claims is higher.

Because the claims encompass the analysis of gene expression in any organism, whereas the specification teaches only the analysis of mouse samples, it is relevant to point out the unpredictability in extrapolating results regarding the asserted association of an allele with a phenotype in humans to any other organism. Similar nucleotide sequences may encode polypeptides with markedly different functionalities. Such a possibility is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs

display distinct functional characteristics (Abstract; pp.39S-40S). Additionally, it is relevant to point out that Hoshikawa et al (2003) teaches unpredictability with regard to applying gene expression results among different organisms. The reference teaches the analysis of gene expression in lung tissue in response to hypoxic conditions which lead to pulmonary hypertension (Fig. 1). The reference teaches that the gene expression profile in mouse is different from that observed in rat (Tables 1-4; p.209 - Abstract). Thus it is unpredictable as to whether or any genes that are rejection-related in, for example, humans are in fact applicable to diagnosing rejection in any other non-human organism.

Because the claims encompass methods for predicting the rejection of any tissue type, where the specification provides only the example of cardiac transplant rejection, it is relevant to note that different gene expression profiles may be related to different tissue rejections. For example, Baan et al (1994) teaches an analysis of cytokine gene expression in tissue rejection, and teaches that IL-2 expression may be indicative of rejections, whereas in liver rejection Il-5 may be a more relevant marker (e.g. p.293, right col.). It is thus unpredictable as to whether or not the profile of the instant specification, asserted to be associated with cardiac tissue rejection, is reliably indicative of the rejection of any other tissue type.

Because the claims encompass the analysis of gene expression in any tissue type, and the comparison of gene expression with any control expression from any tissue, whereas the specification provides only expression in blood samples, it is relevant to point out the unpredictability in comparing gene expression among different

tissues. Cobb et al (2002) teaches the unpredictability in analysis of gene expression in spleen and liver sample from septic mice. Notably, the reference teaches that, when compared to a non-septic sample, the relevant expression profiles of the septic mouse spleen and the septic mouse liver contain different nucleic acids at different levels (Table 1; p.2714, middle col., lns.2-8). Similarly, Flechner et al (2004; citation AD on the IDS of 04/16/2007) teaches that gene expression in blood is different than gene expression in kidney biopsies in an organism with the same phenotype, such as acute rejection (p.1481, left col). It is thus unpredictable as to how one might extrapolate gene expression levels from a blood sample to the analysis of gene expression in a sample obtained from any other source (e.g. any different tissue or organ).

Because the claims encompass detecting any level of gene expression in a sample from an individual and comparing that level to any control level or average level to determine an elevated level that is indicative of rejection, it is relevant to point out the unpredictability associated with gene expression in any individual. Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). Similarly, the prior art of Shalon et al (2001) teaches that preferably 20-50 different test individuals are assayed

to obtain meaningful data showing a significant change in gene expression levels, and changes of gene expression of at least 2 fold and up to 100 fold or more are desirable for the comparison of gene expression levels between a case and control population (p.10 ¶156, ¶158). Finally, Whitney et al teaches that in the analysis of gene expression using microarrays there is considerable intrinsic inter-individual variation in gene expression even in samples within the same environment (Fig 3). It is thus unpredictable as to how robust and reliable any method of detecting tissue rejection in an individual using any increased or elevated level of Gbp1 and Wars expression would be given that the results of the instant specification as based only on comparisons of multiple pooled samples (p.15 of specification) without any analysis of expression levels in individual samples.

And while the generic aspects of the claims, as discussed above, are highly unpredictable, it is further relevant to point out that even a profile consonant with the Election is not established to be reliably indicative of cardiac tissue rejection in humans when examined in blood samples. For example, while the text of the specification asserts that clustering analysis was performed with 40 gene markers disclosed in Table 2 (e.g.: p.32), Table 2 in fact appears to disclose only 33 genes (12 ESTs and 21 named genes). Further, there is no indication in the specification that a clustering analysis using only 5 genes (e.g. as generically encompassed by claim 1) would classify rejection or non-rejection samples with a significant reliability. Given the teachings of the references cited in this rejection, correlation of gene expression with a phenotype is a highly unpredictable endeavor, and without some indication in the specification, there

is in fact no assurance that the minimal gene set, as consonant with the election, would be reliably indicative of cardiac rejection phenotype.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. Such experimentation would require case:control analysis of any tissue type of interest from any organism of interest. Such experimentation would further require the analysis of different types of tissue rejection. Even for the particular assertions presented in the specification, because the specification provides no comparisons or analysis of individual samples, the experimentation would require replication of all the experimentation of the instant specification with the minimal gene sample set as consonant with the Election. Even if such experimentation were to be performed, there is no assurance that the relationships asserted in the specification would be confirmed.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

The Examiner has set forth, in part that the claimed methods are not enabled with regard to the specifically elected gene set. In the event that Applicants may provide a Declaration or some other evidence that the methods are enabled with regard

to the Elected gene set, the Examiner would suggest the following as exemplary claim language to address the other elements of the enablement rejection as set forth in the rejection:

> A method for identifying cardiac transplant tissue rejection in a human subject, said method comprising:
> determining a first gene expression profile in a blood sample taken from said human subject, wherein said first gene expression profile comprises abundances of UQCRB, BTF3, ST13, CUL4A, and CFLAR mRNA; and
> comparing said first gene expression profile to a second gene expression profile, wherein said second gene expression profile comprises the abundances of UQCRB, BTF3, ST13, CUL4A, and CFLAR mRNA in blood samples from a human cardiac transplant population that does not have cardiac tissue rejection;
> wherein a statistically significant increase in UQCRB, BTF3, ST13, CUL4A mRNA abundance in said first gene expression profile compared to said second gene expression profile, and a statistically significant decrease in CFLAR mRNA abundance in said first gene expression profile compared to said second gene expression profile, is indicative of cardiac transplant tissue rejection in the human subject.

Claim Rejections - 35 USC § 102

In the rejection of claims in view of the teachings of the prior art it is recognized that the claims have been rejected under 35 USC 112 1st ¶ for lack of enablement. In the instant case it is noted that while the prior art may teach an embodiment of the required method steps of the claims, and thus anticipate the rejected claims, the prior art is not sufficient to enable the generic scope encompassed by the claims.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 3, 5, and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Ma et al (2001) (WO 2001/81916 A2; as cited on PTO-892 of 04/02/2009).

Regarding claim 1, Ma et al teaches methods of detecting transplant rejection comprising comparison of gene expression profiles that include at least four over-expressed genes and at least on under-expressed gene (e.g.: p.4; p.21; p.30; p.36-37; Table 3; p.76; p.79)

Regarding claims 3 and 5, the reference teaches (e.g.: Table 3) expression that is increased by at least 30% (relevant to claim 3) and expression that is decreased by at least 25% (relevant to claim 5).

Regarding claims 10 and 11, the reference teaches analysis of cardiac allograft rejection (e.g.: p.2; p.61).

Regarding claim 12, the reference teaches analysis using microarrays (e.g. p.16).

Conclusion

13. No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center

will notify applicants of the resolution of the problem within 5-7 business days.

Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634